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Research report

Effects of ibogaine and noribogaine on the antinociceptive action of μ -, δ - and κ -opioid receptor agonists in mice

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Abstract

Ibogaine, an alkaloid isolated from the bark of the African shrub, *Tabernanthe iboga*, has been claimed to decrease the self-administration of drugs of abuse like morphine, cocaine and alcohol. To determine whether these effects are mediated via opioid receptor systems, the effects of ibogaine and its metabolite, noribogaine on the antinociceptive actions of morphine, U-50,488H and [D-Pen²,D-Pen⁵]enkephalin (DPDPE) which are μ -, κ - and δ -opioid receptor agonists, respectively, were determined in male Swiss-Webster mice. Administration of morphine (7 or 10 mg/kg, s.c.), U-50,488H (15 or 25 mg/kg, i.p.) or DPDPE (10 μ g/mouse, i.c.v.) produced antinociception in mice as measured by the tail-flick test. Ibogaine (10, 20 or 40 mg/kg, i.p.) by itself did not alter the tail-flick latency. The same doses of ibogaine injected 10 min before the opioid drugs did not modify the antinociceptive actions of morphine, U-50,488H or DPDPE. Ibogaine administered 4 h or 24 h prior to morphine injection did not modify the antinociceptive action of the latter. A dose of 40 mg/kg (i.p.) of noribogaine enhanced the antinociceptive activity of morphine (10 mg/kg, s.c.). Similarly, the doses of 40 and 80 mg/kg of noribogaine enhanced the antinociception produced by a smaller dose of morphine (5 mg/kg, s.c.). However, antinociception induced by U-50,488H and DPDPE was not modified by noribogaine (10–40 mg/kg). It is concluded that ibogaine, which has been suggested to decrease the self-administration of cocaine and opiates like heroin in humans, does not produce such an action by interacting directly with multiple opioid receptors. However, the metabolite of ibogaine enhances the antinociception of morphine but not of U-50,488H or DPDPE. Thus, in vivo evidence has been provided for the possible interaction of ibogaine with μ -opioid receptor following its metabolism to noribogaine. © 1997 Elsevier Science B.V. All rights reserved.

Keywords: Ibogaine; Noribogaine; Morphine; U-50,488H; DPDPE; Antinociception; Mouse

1. Introduction

Chronic administration of morphine to animals and humans results in the development of tolerance, physical dependence, abstinence syndrome and self-administrative behavior. While a variety of chemicals have been shown to modify various facets of the opiate addiction processes, very few of these agents have reached the stage of clinical trials or use [1]. Ibogaine, an alkaloid isolated from the bark of the African shrub *Tabernanthe iboga*, is claimed to be efficacious in treating heroin addiction in humans [12]. A single oral administration of ibogaine was claimed to have a duration of six months for eliminating the desire to use heroin. Since then a number of investigators have examined the effect of ibogaine on morphine addiction

processes in laboratory animals. Whereas some investigators [4,7,9] found that ibogaine inhibited some symptoms of naloxone-precipitated withdrawal in morphine-dependent rats, Sharpe and Jaffe [16] were unable to demonstrate this effect in rats. Yet other investigators have shown that the incidence of naloxone-induced jumping response in morphine-dependent mice was significantly enhanced by ibogaine [8].

Ibogaine also decreases self-administration of morphine in the rat [10] and this effect appears to be related to the ability of ibogaine to inhibit the morphine-induced increases in dopamine concentration in the extracellular fluid [13]. The exact mechanism, particularly the involvement of opioid receptors, in the inhibitory actions of ibogaine on morphine self-administration or withdrawal syndrome in rodents is still not clear. It is possible that ibogaine may act as an antagonist of opioid receptors. Radioligand-receptor binding studies have yielded contradictory results. The K_i values of ibogaine at the μ -, δ - and κ -opioid receptors

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in bovine cortex were found to be 11.0, > 100 and 3.8 μM , respectively. The putative metabolite of ibogaine, noribogaine, was shown to be about 4 times more potent at the μ -, δ - and κ -opioid receptors [14]. The K_i values indicated that ibogaine or noribogaine is not very potent at the opioid receptors. On the other hand, Codd [5] showed that ibogaine is an agonist at the μ -opioid receptor in the mouse with a K_i value of 130 nM.

In vivo interaction between ibogaine and morphine has been undertaken. Subcutaneous administration of ibogaine (3, 6 or 24 mg/kg) given concurrently with morphine (3 mg/kg) was shown to potentiate the antinociceptive effect of the latter in mice [17].

Since little is known about the direct in vivo interactions between ibogaine, noribogaine and agonists at the multiple opioid receptors other than morphine, the present studies were undertaken to determine the effects of ibogaine and noribogaine in dose ranges which are known to decrease self administration of morphine on μ (morphine)-, κ (U-50,488H)- and δ (DPDPE)-opioid receptor agonist-induced pharmacological actions in the mouse.

2. Materials and methods

2.1. Animals

Male Swiss-Webster mice, weighing 25–30 g (Sasco King Animal Co., Oregon, WI, USA), were housed 5 to a cage in a room with controlled temperature ($23 \pm 1^\circ\text{C}$), humidity ($50 \pm 10\%$) and light (06:00–20:00 h) for at least 4 days before being used. Food and water were made available continuously. All experiments were performed between 10:00 and 15:00 h to minimize diurnal variations.

2.2. Chemicals

Ibogaine HCl, noribogaine HCl and DPDPE were obtained from the National Institute on Drug Abuse, Rockville, MD, USA, through the courtesy of Mr Kevin Gormley and Mr Robert L. Walsh. U-50,488H was a gift of the Upjohn Co., Kalamazoo, MI, USA, through the courtesy of Dr Philip von Voigtlander. Morphine sulfate was purchased from the Mallinckrodt Chemical Co., St. Louis, MO, USA. DPDPE and ibogaine MCI were dissolved in distilled water. Noribogaine HCl was dissolved in 10% DMSO in physiological saline. The other drugs were dissolved in physiological saline. Morphine was injected subcutaneously (s.c.) whereas U-50,488H and ibogaine were injected intraperitoneally (i.p.) in a volume of 10 ml/kg of body weight. DPDPE was injected intracerebroventricularly (i.c.v.) in a volume of 5 μl per mouse according to the method of Haley and McCormick [11].

2.3. Effects of ibogaine on the antinociceptive actions of morphine, U-50,488H or DPDPE in the mouse

The antinociceptive effect of morphine or U-50,488H was measured by the tail-flick test as described earlier

[2,3,6,18]. Briefly, at the beginning of the study, the light intensity in the tail-flick apparatus was adjusted such that the mean basal latencies for the tail-flick response were approximately 2 s. In order to minimize the damage on tail skin tissue damage, the cut-off time was set at 10 s. The tail-flick latencies were determined before and at 30 min intervals for various lengths of time after an injection of morphine (7 or 10 mg/kg) or U-50,488H (15 or 25 mg/kg). The basal tail-flick latencies were subtracted from the effects induced by the drug for each mouse. The tail-flick latencies were plotted as a function of time and the area under the time response curve (AUC) was computed by the trapezoidal method.

To determine the antinociceptive action of DPDPE the tail-flick latencies were measured before and 15 min after an i.c.v. injection of the drug (10 μg per mouse). The basal tail-flick latencies were subtracted from the effect induced by DPDPE. Percentage maximum possible effect (% MPE) was calculated using the following formula: % MPE = [(test latency – control latency)/(10 – control latency)] $\times$ 100. Ten mice were used for each treatment group and the data were expressed as means percentages MPE $\pm$ S.E.M.

The effects of different doses of ibogaine on the antinociceptive response to morphine, U-50,488H or DPDPE were determined. Ibogaine was injected 10 min, 4 h or 24 h before the injection of morphine or U-50,488H and the tail-flick latencies were measured as described above. The antinociceptive response was expressed as AUC for morphine and U-50,488H, and as percentage MPE for DPDPE (means $\pm$ S.E.M.). Ten mice were used for each treatment group. The difference in the antinociceptive response to morphine, U-50,488H or DPDPE in the absence or presence of ibogaine was determined by using the analysis of variance (ANOVA) and Newman-Keuls test. A value of $P < 0.05$ was considered to be significant.

2.4. Effect of noribogaine on the antinociceptive actions of morphine, U-50,488H and DPDPE in the mouse

The effects of three doses of noribogaine (10, 20 or 40 mg/kg) on the antinociceptive response to morphine (10 mg/kg) were determined. Since a dose of 40 mg/kg of noribogaine was shown to produce an enhancement in the antinociceptive action of morphine, the effects of the doses of 20, 40 and 80 mg/kg of noribogaine on the antinociception produced by a lower dose of morphine (5 mg/kg) were investigated. Additionally the effects of noribogaine (10, 20 or 40 mg/kg) on the antinociception produced by U-50,488H (25 mg/kg) and DPDPE (10 μg per mouse) were also determined. The treatment of mice with drugs, the measurement of the antinociceptive response, and the statistical analysis were carried out as described for ibogaine in Section 2.3.

3. Results

3.1. Effects of ibogaine on morphine, U-50,488H and DPDPE-induced antinociception

Subcutaneous administration of morphine (7 or 10 mg/kg) produced antinociception in mice as evidenced by the prolongation of the tail-flick latencies. Ibogaine by itself in doses employed (10, 20 or 40 mg/kg, i.p.) did not alter the tail-flick latency and thus did not produce antinociceptive effect (data not shown). Pretreatment of 10 min with ibogaine (10–40 mg/kg) did not modify morphine-induced antinociceptive response since the $AUC_{0-210 \text{ min}}$ for the antinociceptive action of morphine in the absence and presence of ibogaine did not differ ($P > 0.05$) (Table 1). Similarly, pretreatment with ibogaine (20, 40 or 80 mg/kg) for 4 or 24 h did not alter the antinociception of morphine ($F_{3,36} = 0.14$ for 4 h; $F_{3,36} = 0.49$ for 24 h; $P > 0.05$) (Table 2).

Administration of U-50,488H (15 or 25 mg/kg) produced antinociception in mice which was unaffected by prior treatment with ibogaine (10–40 mg/kg) ($P > 0.05$) (Table 1).

Intracerebroventricular injection of DPDPE induced an antinociceptive response as evidenced by the prolongation

Table 1

Effect of ibogaine on the antinociceptive action of morphine, U-50,488H or DPDPE in mice

Treatment		Antinociceptive activity ^a Mean $\pm$ S.E.M. ($n = 10$)
A.	Morphine (7 mg/kg, s.c.)	
	+ Vehicle	723 $\pm$ 89 ^b
	+ Ibogaine 10 mg/kg, i.p.	799 $\pm$ 93 ^b
	+ Ibogaine 20 mg/kg, i.p.	854 $\pm$ 51 ^b
	+ Ibogaine 40 mg/kg, i.p.	901 $\pm$ 59 ^b
B.	Morphine (10 mg/kg, s.c.)	
	+ Vehicle	1100 $\pm$ 70 ^b
	+ Ibogaine 10 mg/kg, i.p.	1132 $\pm$ 61 ^b
	+ Ibogaine 20 mg/kg, i.p.	1123 $\pm$ 53 ^b
	+ Ibogaine 40 mg/kg, i.p.	1034 $\pm$ 48 ^b
C.	U-50,488H (15 mg/kg, i.p.)	
	+ Vehicle	225 $\pm$ 25 ^b
	+ Ibogaine 10 mg/kg, i.p.	197 $\pm$ 36 ^b
	+ Ibogaine 20 mg/kg, i.p.	265 $\pm$ 42 ^b
	+ Ibogaine 40 mg/kg, i.p.	288 $\pm$ 44 ^b
D.	U-50,488H (25 mg/kg, i.p.)	
	+ Vehicle	802 $\pm$ 32 ^b
	+ Ibogaine 10 mg/kg, i.p.	844 $\pm$ 22 ^b
	+ Ibogaine 20 mg/kg, i.p.	845 $\pm$ 35 ^b
	+ Ibogaine 40 mg/kg, i.p.	855 $\pm$ 20 ^b
E.	DPDPE (10 μ g/mouse, i.c.v.)	
	+ Vehicle	45.7 $\pm$ 8.3 ^c
	+ Ibogaine 10 mg/kg, i.p.	59.5 $\pm$ 12.0 ^c
	+ Ibogaine 20 mg/kg, i.p.	49.7 $\pm$ 12.0 ^c
	+ Ibogaine 40 mg/kg, i.p.	61.5 $\pm$ 7.2 ^c

^a Ibogaine was injected 10 min prior to the injection of morphine, U-50,488H or DPDPE; ^b $AUC_{0-210 \text{ min}}$; ^c percentage MPE.

Table 2

Effect of time of administration of ibogaine on the antinociceptive action of morphine in mice

Treatment before morphine injection (10 mg/kg, s.c.)		Antinociceptive activity ^a Mean $\pm$ S.E.M. ($n = 10$)
A.	4 h	
	+ Vehicle	706 $\pm$ 76
	+ Ibogaine 20 mg/kg, i.p.	675 $\pm$ 67
	+ Ibogaine 40 mg/kg, i.p.	732 $\pm$ 65
	+ Ibogaine 80 mg/kg, i.p.	719 $\pm$ 53
B.	24 h	
	+ Vehicle	643 $\pm$ 60
	+ Ibogaine 20 mg/kg, i.p.	708 $\pm$ 52
	+ Ibogaine 40 mg/kg, i.p.	615 $\pm$ 56
	+ Ibogaine 80 mg/kg, i.p.	663 $\pm$ 55

^a The antinociceptive response was expressed as $AUC_{0-210 \text{ min}}$.

of the tail-flick response. Table 1 shows the effect of different doses of ibogaine on the percentage MPE for the antinociceptive action of DPDPE. None of the doses of ibogaine affected the antinociception induced by DPDPE ($F_{3,36} = 0.57$; $P > 0.05$) (Table 1).

3.2. Effects of noribogaine on the antinociceptive action of morphine, U-50,488H and DPDPE

The effect of noribogaine (10, 20 or 40 mg/kg) on the antinociception induced by a 10 mg/kg dose of morphine is shown in Table 3. Noribogaine produced a significant

Table 3

Effect of noribogaine on the antinociceptive action of morphine, U-50,488H or DPDPE in mice

Treatment		Antinociceptive activity ^a Mean $\pm$ S.E.M. ($n = 10$)
A.	Morphine (5 mg/kg, s.c.)	
	+ Vehicle	621 $\pm$ 41 ^b
	+ Noribogaine 20 mg/kg, i.p.	770 $\pm$ 109 ^b
	+ Noribogaine 40 mg/kg, i.p.	989 $\pm$ 76 ^{b,e}
	+ Noribogaine 80 mg/kg, i.p.	1018 $\pm$ 110 ^{b,e}
B.	Morphine (10 mg/kg, s.c.)	
	+ Vehicle	727 $\pm$ 99 ^b
	+ Noribogaine 10 mg/kg, i.p.	813 $\pm$ 147 ^b
	+ Noribogaine 20 mg/kg, i.p.	934 $\pm$ 142 ^b
	+ Noribogaine 40 mg/kg, i.p.	1278 $\pm$ 148 ^{b,e}
C.	U-50,488H (25 mg/kg, i.p.)	
	+ Vehicle	564 $\pm$ 63 ^c
	+ Noribogaine 10 mg/kg, i.p.	483 $\pm$ 66 ^c
	+ Noribogaine 20 mg/kg, i.p.	534 $\pm$ 64 ^c
	+ Noribogaine 40 mg/kg, i.p.	544 $\pm$ 92 ^c
D.	DPDPE (10 μ g/mouse, i.c.v.)	
	+ Vehicle	67.7 $\pm$ 13.7 ^d
	+ Noribogaine 10 mg/kg, i.p.	55.1 $\pm$ 12.5 ^d
	+ Noribogaine 20 mg/kg, i.p.	54.0 $\pm$ 12.5 ^d
	+ Noribogaine 40 mg/kg, i.p.	61.4 $\pm$ 12.3 ^d

^a Noribogaine was injected 10 min prior to the injection of morphine, U-50,488H or DPDPE; ^b $AUC_{0-300 \text{ min}}$; ^c $AUC_{0-240 \text{ min}}$; ^d percentage MPE. ^e $P < 0.05$ vs. vehicle-injected controls.

effect on morphine-induced antinociception ($F_{3,36} = 3.19$; $P < 0.05$). Noribogaine in 10 and 20 mg/kg doses did not modify antinociception induced by morphine (10 mg/kg). However, a dose of 40 mg/kg significantly enhanced morphine antinociception ($q_{36,4} = 4.07$; $P < 0.05$). The effect of a slightly higher doses of noribogaine (20, 40 or 80 mg/kg) on antinociception induced by a lower dose of morphine (5 mg/kg) was also determined. ANOVA indicated a significant interaction ($F_{3,36} = 4.44$; $P < 0.05$) (Table 3). Both the 40 and 80 mg/kg doses of noribogaine significantly enhanced morphine-induced antinociception ($q_{36,3} = 4.12$; $q_{36,4} = 4.44$; $P < 0.05$); but the lower dose of 20 mg/kg did not modify it. U-50,488H and DPDPE-induced antinociception was unaffected by noribogaine (10, 20 or 40 mg/kg) ($P > 0.05$) (Table 3).

4. Discussion

The present studies demonstrate that ibogaine does not modify morphine-induced antinociception in mice. Ibogaine by itself did not alter the tail-flick latency and thus did not induce an antinociceptive response. The effects of ibogaine on the antinociceptive response to two doses of morphine, i.e. 7 or 10 mg/kg, were determined with the hope that any change caused by ibogaine could be detected, however, ibogaine failed to show any effect. In a previous study, ibogaine in doses of 3, 6 or 24 mg/kg given subcutaneously along with 3 mg/kg of morphine potentiated the antinociceptive effect of the latter in mice. The effect of ibogaine was apparently dose-dependent [17]. In our studies we have repeated the experiments several times with different doses of morphine and ibogaine and failed to find any effect of ibogaine on morphine antinociception. Our results on the antinociceptive effect of ibogaine are similar to those of Schneider and McArthur [17] and of Frances et al. [8] who did not find any antinociceptive effect of ibogaine up to a dose of 40 mg/kg. The reason for the discrepancy between the present study and that of Schneider and McArthur [17] on the interaction of ibogaine and morphine is not evident at present.

Ibogaine by itself did not alter the colonic temperature nor did it modify the lowering of the colonic temperature induced by morphine (data not shown). Thus, ibogaine does not appear to modify the two pharmacological actions of morphine. Similar effects were observed on κ -opioid agonist-induced antinociception and hypothermia and δ -opioid receptor agonist-induced antinociception.

The present studies also indicate that noribogaine, a metabolite of ibogaine, potentiates the antinociceptive actions of morphine but not those of κ - and δ -opioid receptor agonists. Since ibogaine does not modify μ -, κ - and δ -opioid receptor agonist-induced antinociception, it would appear that it does not directly interact with multiple opioid receptors in vivo. The question arises as to what are the potential mechanisms in its ability to modify self-ad-

ministration of opioid drugs like heroin. Do these mechanisms involve opioid or non-opioid systems? Several in vitro radioligand-binding studies have been carried out to determine the effect of ibogaine on opioid and non-opioid receptors of the brain tissue. In vitro binding studies revealed that ibogaine had poor affinity for the binding of [3 H]ligands of opioid receptors in bovine cortex with K_i values 11.0, > 100 and $3.77 \mu\text{M}$ for μ -, δ - and κ -opioid receptors, respectively. However, noribogaine, showed higher affinity than the parent compound for opioid receptors with K_i values of 2.66, 24.72 and $0.96 \mu\text{M}$ at the μ -, δ - and κ -opioid receptors, respectively [14]. Thus, noribogaine was, in general, 4 times as potent as ibogaine at the opioid receptors. Another study using [3 H]naloxone as the opioid receptor ligand and using a two-site model revealed ibogaine to be an agonist at the μ -opioid receptor in mouse forebrain with a K_i value of 130 nM [5]. [3 H]Naloxone is a rather non-selective ligand for the μ -opioid receptor whereas the ligands employed by Pearl et al. [14] were more selective. It is interesting to note that both ibogaine and noribogaine had greater affinity towards κ -opioid receptors relative to μ - and δ -receptors, yet they did not affect κ -opioid receptor agonist-induced antinociception in the mouse. Based on these studies, it appears that ibogaine itself has poor affinity for the opioid receptor but its metabolite appears to have a greater affinity for the opioid receptors. However, a 4-fold greater affinity of noribogaine for opioid receptors compared to ibogaine can not account for the in vivo effects observed in the present study. The anti-addictive action of ibogaine may be partially mediated via its active metabolite.

Ibogaine also appears to interact with non-opioid receptors. For instance, ibogaine was shown to be a competitive inhibitor of [3 H]MK-801 binding to *N*-methyl-D-aspartate (NMDA) receptor-coupled ion channels [15]. Although NMDA receptor antagonists block tolerance to opioid drugs, they have little or no effect on the development of physical dependence and withdrawal symptoms [1].

In summary, the present studies demonstrate that ibogaine does not affect the acute responses to multiple opioid receptor agonists and compliment the ligand binding studies in vitro. However, noribogaine potentiates the antinociceptive action of morphine but not those of κ - and δ -opioid receptors. Therefore, it is possible that the anti-addictive property of ibogaine may be mediated via its metabolite(s).

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